

CLAIMS

1. A method of inducing tolerance to a therapeutic cell in a patient who is to be administered subsequently a therapeutic amount of the said therapeutic cell or a precursor thereof, the method comprising administering to the patient (a) a tolerising cell sharing the same antigenic characteristics as the therapeutic cell, or an antigen found thereon or a derivative of said antigen, and (b) an agent which raises the effective cAMP concentration in a monocyte cell.
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- 10 2. A method of reducing the risk of rejection of a transplant in a patient in need of transplantation of a therapeutic cell for cell or tissue regeneration, the method comprising administering to the patient prior to the transplant (a) a tolerising cell sharing the same antigenic characteristics as the therapeutic cell which therapeutic cell is, or is able to differentiate into, the cell or tissue to be regenerated, or an antigen found thereon or a derivative of said antigen, and (b) an agent which raises the effective cAMP concentration in a monocyte cell.
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- 20 3. A method of treating a patient in need of cell or tissue regeneration the method comprising administering to the patient (a) a tolerising cell sharing the same antigenic characteristics as the therapeutic cell to be administered subsequently which therapeutic cell is, or is able to differentiate into, the cell or tissue to be regenerated, or an antigen found thereon or a derivative of said antigen, (b) an agent which raises the effective cAMP concentration in a monocyte cell in an amount to induce tolerance to the said therapeutic cell, and subsequently administering to the patient (c) a therapeutic amount of the said therapeutic cell.
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- 30 4. A method according to Claim 3 wherein in step (a) a cell is administered to the patient.

5. A method according to Claim 4 wherein the tolerising cell in step (a) and the therapeutic cell in step (c) are derived from the same parent embryonic stem cell.
- 5 6. A method according to any one of claims 1 to 5 wherein the patient is additionally administered granulocyte-macrophage colony stimulating factor (GMCSF) or a derivative thereof.
- 10 7. A method according to any one of the preceding claims wherein the patient is suffering from a degenerative disease or disorder.
- 15 8. A method according to Claim 7 wherein the degenerative disease or disorder is selected from the group consisting of diabetes, stroke, Parkinson's disease, ALS (Lou Gehrig's disease), spinal cord injury, heart attack, cardiac ischaemia, congestive heart failure, hepatitis, cirrhosis, cancer, immunodeficiency, osteoporosis, osteoarthritis, macular degeneration, burn, wounds, muscular dystrophy and multiple sclerosis.
9. A method according to any one of the preceding claims wherein (a) the tolerising cell or an antigen found thereon or a derivative of said antigen, and
20 (b) the agent which raises the effective cAMP concentration in a monocyte cell are administered together.
- 25 10. A method according to Claim 9 wherein GMCSF is administered at the same time as (a) the tolerising cell, or an antigen found thereon or a derivative of said antigen, and (b) the agent which raises the effective cAMP concentration in a monocyte cell.
- 30 11. A method according to any one of Claims 1 to 10 wherein (a) the tolerising cell or an antigen found thereon or a derivative of said antigen is administered after administration of (b) the agent which raises the effective cAMP

concentration in a monocyte cell and, if used, the GMCSF or derivative thereof.

12. Use of a combination of (a) a tolerising cell sharing the same antigenic characteristics as the therapeutic cell to be administered therapeutically, or an antigen found thereon or a derivative of said antigen and (b) an agent which raises the effective cAMP concentration in a monocyte cell, in the manufacture of a medicament for inducing tolerance to a therapeutic cell in a patient who is to be administered subsequently a therapeutic amount of the

10 said therapeutic cell or a precursor thereof.

13. Use of a tolerising cell sharing the same antigenic characteristics as a therapeutic cell to be administered therapeutically, or an antigen found thereon or a derivative of said antigen in the manufacture of a medicament for inducing tolerance to a therapeutic cell in a patient who is to be administered subsequently a therapeutic amount of the said therapeutic cell wherein the patient is administered an agent which raises the effective cAMP concentration in a monocyte cell.

20 14. Use of an agent which raises the effective cAMP concentration in a monocyte cell in the manufacture of a medicament for inducing tolerance to a therapeutic cell in a patient who is to be administered subsequently a therapeutic amount of the said therapeutic cell wherein the patient is administered a tolerising cell sharing the same antigenic characteristics as the therapeutic cell to be administered therapeutically, or an antigen found thereon or a derivative of said antigen.

25 15. Use of any one or two of (a) a tolerising cell sharing the same antigenic characteristics as the therapeutic cell to be administered therapeutically, or an antigen found thereon or a derivative of said antigen, (b) an agent which raises the effective cAMP concentration in a monocyte cell and (c) GMCSF, in the manufacture of a medicament for inducing tolerance to the therapeutic

cell in a patient who is to be administered subsequently a therapeutic amount of the therapeutic cell, and who is administered one or both of (a), (b) or (c) which is not found in the medicament as said.

- 5 16. Use of a combination of (a) a tolerising cell sharing the same antigenic characteristics as a therapeutic cell which therapeutic cell is, or is able to differentiate into, the cell or tissue to be regenerated, or an antigen found thereon or a derivative of said antigen, and (b) an agent which raises the effective cAMP concentration in a monocyte cell, in the manufacture of a
10 medicament for reducing the risk of rejection of a transplant in a patient in need of transplantation of a therapeutic cell for cell or tissue regeneration.
- 15 17. Use of a tolerising cell sharing the same antigenic characteristics as a therapeutic cell which therapeutic cell is, or is able to differentiate into, the cell or tissue to be regenerated, or an antigen found thereon or a derivative of said antigen in the manufacture of a medicament for reducing the risk of rejection of a transplant in a patient in need of transplantation of a therapeutic cell for cell or tissue regeneration wherein the patient is administered an agent which raises the effective cAMP concentration in a monocyte cell.
- 20 18. Use of an agent which raises the effective cAMP concentration in a monocyte cell in the manufacture of a medicament for reducing the risk of rejection of a transplant in a patient in need of transplantation of a therapeutic cell for cell or tissue regeneration wherein the patient is administered a tolerising cell sharing the same antigenic characteristics as the therapeutic cell which therapeutic cell is, or is able to differentiate into, the cell or tissue to be regenerated, or an antigen found thereon or a derivative of said antigen.
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- 30 19. Use of any one or two of (a) a tolerising cell sharing the same antigenic characteristics as a therapeutic cell which therapeutic cell is, or is able to differentiate into, the cell or tissue to be regenerated, or an antigen found thereon or a derivative of said antigen, (b) an agent which raises the effective

cAMP concentration in a monocyte cell and (c) GMCSF in the manufacture of a medicament for reducing the risk of rejection of a transplant in a patient in need of transplantation of a therapeutic cell for cell or tissue regeneration, and who is administered one or both of (a), (b) or (c) which is not found in the medicament as said.

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20. Use of a combination of (a) a tolerising cell sharing the same antigenic characteristics as the therapeutic cell to be administered subsequently which therapeutic cell is, or is able to differentiate into, the cell or tissue to be regenerated, or an antigen found thereon or a derivative of said antigen, and (b) an agent which raises the effective cAMP concentration in a monocyte cell in the manufacture of a medicament for treating a patient in need of cell or tissue regeneration, wherein the patient is subsequently administered a therapeutic amount of the said therapeutic cell.
 - 10 21. Use of a tolerising cell sharing the same antigenic characteristics as the therapeutic cell to be administered subsequently which therapeutic cell is, or is able to differentiate into, the cell or tissue to be regenerated, or an antigen found thereon or a derivative of said antigen in the manufacture of a medicament for treating a patient in need of cell or tissue regeneration wherein the patient is administered an agent which raises the effective cAMP concentration in a monocyte cell and is subsequently administered a therapeutic amount of the said therapeutic cell.
 - 15 22. Use of an agent which raises the effective cAMP concentration in a monocyte cell in the manufacture of a medicament for treating a patient in need of cell or tissue regeneration wherein the patient is administered a tolerising cell sharing the same antigenic characteristics as the therapeutic cell to be administered subsequently which therapeutic cell is, or is able to differentiate into, the cell or tissue to be regenerated, or an antigen found thereon or a derivative of said antigen and is subsequently administered a therapeutic amount of the said therapeutic cell.
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23. Use of any one or two of (a) a tolerising cell sharing the same antigenic characteristics as the therapeutic cell to be administered subsequently which therapeutic cell is, or is able to differentiate into, the cell or tissue to be regenerated, or an antigen found thereon or a derivative of said antigen, (b) an agent which raises the effective cAMP concentration in a monocyte cell and (c) GMCSF or a derivative thereof in the manufacture of a medicament for treating a patient in need of cell or tissue regeneration, and who is administered one or two of (a), (b) or (c) which is not found in the medicament as said, wherein the patient is subsequently administered a therapeutic amount of the said therapeutic cell.
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24. Use of a therapeutic amount of a therapeutic cell which is, or is able to differentiate into, a cell or tissue to be regenerated in the manufacture of a medicament for treating a patient in need of cell or tissue regeneration, wherein the patient has previously been administered (a) a tolerising cell sharing the same antigenic characteristics as the therapeutic cell, or an antigen found thereon or a derivative of said antigen and (b) an agent which raises the effective cAMP concentration in a monocyte cell and, optionally, (c) GMCSF.
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25. A composition for inducing tolerance to a therapeutic cell in a patient who is to be administered subsequently a therapeutic amount of the said therapeutic cell or a precursor thereof comprising (a) a tolerising cell sharing the same antigenic characteristics as the therapeutic cell, or an antigen found thereon or a derivative of said antigen, (b) an agent which raises the effective cAMP concentration in a monocyte cell, optionally, (c) granulocyte-macrophage colony stimulating factor (GMCSF) or a derivative thereof.
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26. A therapeutic system for inducing tolerance to a therapeutic cell in a patient who is to be administered subsequently a therapeutic amount of the said therapeutic cell or a precursor thereof comprising (a) a tolerising cell sharing the same antigenic characteristics as the therapeutic cell, or an antigen found
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thereon or a derivative of said antigen, (b) an agent which raises the effective cAMP concentration in a monocyte cell, optionally, (c) granulocyte-macrophage colony stimulating factor (GMCSF) or a derivative thereof.

- 5 27. A kit of parts for inducing tolerance to a therapeutic cell in a patient who is to be administered subsequently a therapeutic amount of the said therapeutic cell or a precursor thereof comprising (a) a tolerising cell sharing the same antigenic characteristics as the therapeutic cell, or an antigen found thereon or a derivative of said antigen, (b) an agent which raises the effective cAMP concentration in a monocyte cell, optionally, (c) granulocyte-macrophage colony stimulating factor (GMCSF) or a derivative thereof.
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- 15 28. A method according to any of Claims 1 to 11, a use according to any of Claims 11 to 24, a composition according to Claim 25, a therapeutic system according to Claim 26 or a kit of parts according to Claim 27 wherein the agent which raises the effective cAMP concentration in a monocyte cell is any one or more of a prostaglandin or agonist thereof, a β -adrenergic agent, a blocker of cAMP export from the cell, forskolin or a derivative thereof, a cAMP phosphodiesterase inhibitor, a cAMP analogue, or cholera toxin or a derivative or fragment thereof.
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- 25 29. A method or use or composition or therapeutic system or kit of parts according to Claim 28 wherein the blocker of cAMP export from the cell is probenecid or progesterone.
- 30 30. A method or use or composition or therapeutic system or kit of parts according to Claim 28 wherein the cAMP analogue is Sp-adenosine 3',5'-cyclic monophosphorothioate or 8-bromoadenosine 3',5' cyclic monophosphate or dibutyryl cAMP.

31. A method or use or composition or therapeutic system or kit of parts according to Claim 28 wherein the prostaglandin or agonist thereof stimulates cAMP production in a monocyte.
- 5 32. A method or use or composition or therapeutic system or kit of parts according to according to Claim 28 or 31 wherein the prostaglandin or agonist thereof is any one of a prostaglandin E, such as prostaglandin E₂ or an analogue thereof, dinoprostone, gemeprost, misoprostol, alprostadil, limaprost, butaprost, 11-deoxy PGE1, AH23848, AH13205, or a 19-hydroxy PGE.
- 10 33. A method according to Claim 6 or a use according to any of Claims 15 or 19 or 23 or a composition according to Claim 25 or a therapeutic system according to Claim 26 or a kit of parts according to Claim 27 wherein the GMCSF, if present, is human GMCSF having the amino acid sequence as defined in Figure 1, or naturally occurring variants thereof.
- 15 34. A method or use or composition or therapeutic system or kit of parts according to Claim 33 wherein the GMCSF is sargramostim.
- 20 35. A method according to any of Claims 1 to 11 comprising administering a monocyte chemotactic agent to the patient.
- 25 36. A method according to Claim 35 wherein the monocyte chemotactic agent is MCP-1 or MIP-1 α .
37. A method according to any of Claims 1 to 11 comprising administering a PDE inhibitor to the patient.
- 30 38. A method or use or composition or therapeutic system or kit of parts according to Claim 28 wherein the PDE inhibitor is any one of 3-isobutyl-1-methylxanthine (IBMX), pentoxifylline (3,7-dihydro-3,7-dimethyl-1-(5-

oxohexyl)-1H-purine-2,6-dione), rolipram (4-[3-cyclopentyloxy-4-methoxyphenyl]-2-pyrrolidinone), CP80 633, CP102 995, CP76 593, Ro-20-1724 (4-[3-butoxy-4-methoxybenzyl]-2-imidazolidinone), theophylline, or denbufylline (1,3-di-n-butyl-7-(2-oxopropyl)-xanthine).

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39. A method or use or composition or therapeutic system or kit of parts according to Claim 38 wherein the PDE inhibitor is selective for type IV PDE.

10 40. A method or use or composition or therapeutic system or kit of parts according to Claim 39 wherein the PDE inhibitor selective for type IV PDE is any one of rolipram (4-[3-cyclopentyloxy-4-methoxyphenyl]-2-pyrrolidinone), CP80 633, CP102 995, CP76 593, Ro-20-1724 (4-[3-butoxy-4-methoxybenzyl]-2-imidazolidinone), denbufylline (1,3-di-n-butyl-7-(2-oxopropyl)-xanthine), or CDP840, RP73401 or RS33793.

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41. A pharmaceutical composition comprising the composition according to Claim 25 and a pharmaceutically acceptable carrier, diluent or excipient.

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42. A composition according to Claim 25 for use in medicine.

43. A therapeutic system according to Claim 26 or a kit of parts according to Claim 27 further comprising a therapeutic cell which is, or is able to differentiate into, a cell or tissue to be regenerated.

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44. Any novel method of pretolerising a patient to a cell as described herein.

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45. Any novel method of pretolerising a patient to a cell as described herein, wherein the patient is subsequently administered a therapeutic amount of the cell or a precursor thereof in order to regenerate cells or tissue in the patient.